Bendamustine-based conditioning prior to autologous stem cell transplantation is associated with high rate of febrile neutropenia and higher mortality

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Dear Editor,

We have read the paper by Chantepie et al.[1] evaluating safety of benadamustine-based conditioning prior to autologous stem cell transplantation (ASCT) with great interest. Authors reported concerningly high frequency of acute renal failure (27.9%) and high rates of other toxicities observed with BeEAM (bendamustine, etoposide, cytarabine, melphalan) conditioning regimen. Shortage of carmustine led to replacement of standard BEAM (carmustine, etoposide, cytarabine, melphalan) with BeEAM conditioning regimen in our institution as well. High frequency of febrile netropenia and increased mortality that we observed prompted us to further compare toxicities and outcomes between these two regimens which we report here.

We retrospectively analysed a cohort of 60 ASCT patients 18 years or older with histologically confirmed diagnosis of Non-Hodgkin or Hodgkin lymphoma that received either BEAM (43 patients) or BeEAM myeloablative regimen (17 patients) as a part of the ASCT procedure in the period from 2008 to 2018. Bendamustine doses of 200mg/m^2/day were used. Acute kidney injury was defined according to KDIGO guidelines as in the paper by Chantepie et al.[1] Numerical variables were expressed as median and interquartile range (IQR) and were compared between two groups using the Mann-Whitney-U test. Categorical variables were expressed as percentages and were compared between two groups using the Fisher test or X^2 test where appropriate. Survival analysis was based on the Kaplan-Meier method, the Cox-Mantel version of the log-rank test was used to compare survival between two groups. P values <0.05 were considered statistically significant. Analyses were done using the MedCalc statistical program ver. 18.10 (MedCalc Software bvba, Ostend, Belgium).

Median age was 51.5 years, a majority of patients had diffuse large B-cell lymphoma (53%). Patients' characteristics and outcomes are shown in the Table. BEAM and BeEAM groups did not differ regarding age, gender, diagnosis, baseline estimated creatinine clearance, duration of hospitalization, time to neutrophil or platelet recovery (P>0.05 for all comparisons) showing that two regimens were comparable in terms of baseline and engraftment characteristics. However, patients receiving bendamustine were significantly more likely to develop acute kidney injury (23.5% vs 0% for BeEAM vs BEAM, respectively; P=0.005), virtually all experienced febrile neutropenia (100% vs 74% for BeEAM vs BEAM, respectively; P=0.025) and were more likely to require intensive-care-unit (ICU) management (23.5% vs 0% for BeEAM vs BEAM, respectively; P=0.005). Most worrisome, patients receiving bendamustine experienced significantly higher 100-day mortality (17.6% vs 0% for BeEAM vs BEAM, respectively; P=0.004) as shown in the Figure. All three deaths observed in the bendamustine group were due to septic complications.

It should be noted that high rates of ICU admission (24%) and renal toxicity (17%) were observed with BeEAM by other author groups as well.[2] Although limited by small numbers, retrospective design and single center experience, our findings complement previously reported results by Chantepie and others, and raise serious concerns about safety of benadmustine-based conditioning prior to ASCT. We resorted to alternative conditioning regimen based on lomustine (LEAM – lomustine, etoposide, cytarabine, melphalan) until additional evidence regarding efficacy/safety of currently available regimens, or new treatment options emerge.

References:

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Table 1: Patient's characteristics and outcomes in patients receiving BEAM and BeEAM myeloablative regimens prior to autologous stem cell transplantation.

	BEAM	BeEAM	P value
Total number	43	17	-
Age /years	52 IQR (38.5 - 59)	50 IQR (39 - 56)	0.825
Gender			
Male gender	24/43 (55.8%)	8/17 (47.1%)	
Female gender	19/43 (44.2%)	9/17 (52.9%)	0.540
Diagnosis			
DLBCL	20/43 (45.2%)	10/17 (56.3%)	
Mantle cell	4/43 (9.5%)	2/17 (12.5%)	
Burkitt	1/43 (2.4%)	0/17 (0%)	
T-NHL	4/43 (9.5%)	2/17 (12.5%)	
Indolent B-NHL	8/43 (19%)	1/17 (6.3%)	
Hodgkin lymphoma	6/43 (14.3%)	2/17 (12.5%)	0.811
MDRD estimated creatinine clearance /mlmin^{-1}1.73m^{-2}	88 IQR (75.5 - 100.5)	108 IQR (80 - 122)	0.212
Duration of hospitalization /days	25 IQR (21 - 28.5)	25 IQR (23 - 32)	0.320
Neutrophil recovery /days	10 IQR (9 - 11)	10 IQR (9 - 10)	0.503
Platelets recovery /days	12 IQR (10.5 - 14)	12.5 IQR (11.3 - 16.5)	0.294
Acute kidney injury	**0/43 (0%)**	**4/17 (23.5%)**	**0.005***
Febrile neutropenia	**32/43 (74.4%)**	**17/17 (100%)**	**0.025***
Isolated pathogen	27/43 (62.8%)	15/17 (88.2%)	0.053
Need for intensive care unit	**0/43 (0%)**	**4/17 (23.5%)**	**0.005***
100-days mortality	**0/43 (0%)**	**3/17 (17.6%)**	**0.004***

IQR – interquartile range; numerical variables were compared using the Mann-Whitney U test; categorical variables were compared using the Fisher test of X^2 test where appropriate; mortality was analysed using the Cox-Mantel version of the log-rank test.

Figure 1: 100-days mortality post autologous stem cell transplantation stratified by the myeloablative regimen (BEAM / BeEAM).